# Evaluation of the effects of penicillin G potassium and potassium chloride on the motility of the large intestine in horses

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**Objective**—To evaluate effects of IV administration of penicillin G potassium (KPEN) or potassium chloride (KCl) on defecation and myoelectric activity of the cecum and pelvic flexure of horses.

**Animals**—5 healthy horses.

**Procedure**—Horses with 12 bipolar electrodes on the cecum and pelvic flexure received KPEN or KCl solution by IV bolus 4 hours apart. Each horse received the following: $2 \times 10^7$ U of KPEN (high-dose KPEN) followed by 34 mEq of KCl (high-dose KCl), $1 \times 10^7$ U of KPEN (low-dose KPEN) followed by 17 mEq of KCl (low-dose KCl), high-dose KCl followed by high-dose KPEN, and low-dose KCl followed by low-dose KPEN. Number of defecations and myoelectric activity were recorded for 60 minutes. The first three 5-minute segments and first four 15-minute segments of myoelectric activity were analyzed.

**Results**—Number of defecations during the first 15-minute segment was greater after high-dose KPEN treatment than after high-dose or low-dose KCl treatment. Compared with reference indexes, myoelectric activity was greater in the pelvic flexure for the first 5-minute segment after high-dose KCl treatment, in the cecum and pelvic flexure for the first 5-minute segment and in the pelvic flexure for the first 15-minute segment after low-dose KPEN treatment, and in the pelvic flexure for the first and second 5-minute segments and the first three 15-minute segments after high-dose KPEN treatment.

**Conclusions and Clinical Relevance**—IV administration of KPEN stimulates defecation and myoelectric activity of the cecum and pelvic flexure in horses. Effects of KPEN may be beneficial during episodes of ileus. (*Am J Vet Res* 2003;64:1360–1363)

Diarrhea has been reported as an adverse effect of antibiotic administration, including penicillin, in people and horses.[1-3] Anecdotally, horses frequently defecate within minutes after IV injection of **penicillin G potassium (KPEN)**. Erythromycin and other macrolide antibiotics have been shown to have prokinetic effects on the gastrointestinal tract of several species, including horses.[4-9] Although the macrolides share a similar spectrum of antimicrobial activity with the penicillins, their molecular structure is quite different, and there is no reason to suspect that the mechanism of action on the motility of the gastrointestinal tract would be similar. The antibiotic drugs streptomycin, chloramphenicol, and tetracycline have been shown to have prokinetic effects on smooth muscle tissue in vitro, but sodium penicillin was without effect in the same study.[10] Chlortetracycline had a stimulatory effect on motility in dogs in vivo and rabbits in vitro.[11] Other antibiotics, including clindamycin, gentamicin, pivmecillinam, kanamycin, and trimethoprim, have been shown to decrease the peristaltic response in vitro.[12]

In vitro, excess extracellular potassium can lower the resting membrane potential of smooth muscle cells and result in lowering the threshold of initiation of an action potential and subsequent muscular contraction.[13] Bolus administration of $K^+$ could potentially have the same effect in vivo, resulting in intestinal smooth muscle contraction. Thus, effects of KPEN on intestinal motility could be attributed to bolus administration of the potassium ion itself. The purpose of the study reported here was to evaluate the effect of KPEN or **potassium chloride (KCl)** administration on defecation and motility of the cecum and pelvic flexure in horses.

## Materials and Methods

Experimental protocol—The experimental protocol was reviewed and approved by the Texas A&M University Laboratory Animal Care Committee. Four mature geldings and 1 mare (2 Thoroughbreds and 3 Quarter Horses) weighing between 461 and 547 kg were used. Feed and water were withheld for 24 hours, and horses were then anesthetized with xylazine hydrochloride (1.1 mg/kg, IV), ketamine hydrochloride (2.2 mg/kg, IV), and diazepam (0.015 mg/kg, IV). Anesthesia was maintained with inhalation of sevoflurane (3.5 to 5.5%) in oxygen. A ventral midline celiotomy was performed, and 16 bipolar electrodes were introduced into the smooth muscle of the ileum, cecum, and pelvic flexure, as previously described.[9] The 4 ileal electrodes were used in a different experiment. The surgical protocol involved induction of postoperative ileus by vigorous rubbing of the small intestine.[9]

Amikacin (16 mg/kg) or gentamicin (6.6 mg/kg) was administered IV immediately prior to surgery and once daily for 4 to 5 days after surgery. Several horses also received metronidazole (10 mg/kg, PO, q 12 h) for 3 to 10 days after surgery. After surgery, horses were gradually returned to their regular ration, which consisted of free-choice coastal Bermuda grass hay and grain mix twice daily.

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Another study was performed on these horses during the postoperative period. The study reported here began at least 15 days postoperatively in all horses and at least 7 days after the conclusion of the other study. All horses were clinically normal at the time of the experiments. Horses were not given any grain the morning of the recording session, but had ad libitum access to hay throughout the session. Myoelectric activity of the cecum and pelvic flexure was recorded for 1 hour to determine that normal-appearing patterns were present and to establish a reference period against which to compare the effect of treatment.

In random order on 4 separate days, each horse received the following 4 series of KPEN and KCl (IV, over 30 seconds): **$2 \times 10^7$ U of KPEN (high-dose KPEN)** followed in 4 hours by **34 mEq of KCl (high-dose KCl)**, **$1 \times 10^7$ U of KPEN (low-dose KPEN)** followed in 4 hours by **17 mEq of KCl (low-dose KCl)**, high-dose KCl followed in 4 hours by high-dose KPEN, and low-dose KCl followed in 4 hours by low-dose KPEN, with at least 1 day between experiments. The amount of $K^+$ administered (17 and 34 mEq) and the volume injected (20 and 40 mL) were the same for both of the low-dose treatments and both of the high-dose treatments, respectively.

Defecations were recorded for 60 minutes following each injection, but because defecations were infrequent after 15 minutes after injection, only the first 15-minute segment after injection was analyzed. Myoelectric activity was recorded by use of a data acquisition software package.[a] Data were stored on disks[b] until analyzed. Digitized myoelectric signals for each of the channels were processed by use of computer software[c] prior to analysis. The signal was rectified, and the baseline was then adjusted to eliminate electrical noise. The design of the experiment called for 4 recording sessions. Not all horses had functioning electrodes for a sufficient time to complete all sessions. Three of the horses completed all 4 sessions, 1 horse completed 3 sessions, and 1 horse completed 2 sessions. The recordings were examined, and channels with electrodes that were producing artifacts were removed from the analysis for that day. Six electrodes were implanted on the cecum, and 6 were implanted on the pelvic flexure during preparation of the horses. The signal was of sufficient quality on average from 4 cecal and 4.8 pelvic flexure electrodes/session. Signals were integrated in 5-minute intervals to obtain activity indices, and these values were downloaded to a spreadsheet. Time of administration of drug was designated time 0. Activity indices for the first 15 minutes after drug administration (divided into three 5-minute segments) and the first hour after drug administration (divided into four 15-minute segments) were analyzed.

**Data analysis**—The number of defecations was compared by use of a generalized linear models approach with horses modeled as random effects and treatment as fixed effects, followed by the Duncan multiple range test.[11] Each treatment was analyzed separately, then data from the 2 KPEN treatments were pooled and compared with the 2 KCl treatments.

Myoelectric data were analyzed separately for the cecum and pelvic flexure. The activity indices for the test segments were compared with the activity index of the reference period, which was based on the myoelectric activity during the 60 minutes prior to drug administration. The 5-minute reference activity index was obtained by dividing the total activity for 60 minutes by 12. The 15-minute reference activity index was obtained by dividing the total activity for 60 minutes by 4. For each test segment, the activity index was divided by the appropriate reference activity index and expressed as a proportion. The reference activity index value was always 1. A value > 1 indicated an increase in activity, whereas a value < 1 indicated a decrease in activity. The values were compared by use of a generalized linear models approach with horses modeled as random effects, electrodes modeled as fixed effects nested within horses, and time periods modeled as fixed effects.[11] The Duncan multiple range test was used to analyze differences between periods.[11]

To determine whether the occurrence of **colonic migrating myoelectric complexes (CMMCs)** was associated with the injection of either KCl or KPEN, each session was evaluated visually for CMMCs by 1 of the authors (AJR) without knowledge of the treatment or the exact time of injection. All CMMCs were identified, and the time at the beginning of the CMMC recorded. Then the sessions were divided into 10 periods of 10 minutes each beginning 50 minutes before the time of injection and extending for 50 minutes after. The rationale for evaluating the 50 minutes before and after injection was that a CMMC might have been difficult to identify if it developed in the first or last 10 minutes of the 2-hour recording session because it could have been partially missing from the recording. The frequency of occurrence of a CMMC in the period immediately following the administration of a treatment was compared with the frequency of occurrence of a CMMC in the periods during the same recording sessions that were not associated with administration of a treatment by use of a paired *t* test. For all comparisons, a value of $P < 0.05$ was considered significant.

## Results

**Clinical observations**—No adverse effects of drug administration were observed for either KPEN or KCl. In the first 15 minutes following KPEN administration, 41 defecations were recorded from a horse. Only 8 were recorded during the next 45 minutes. Therefore, only data from the first 15 minutes were analyzed.

Mean (± SD) number of defecations in the first 15 minutes after injection was significantly greater for high-dose KPEN treatment (2.2 ± 1.44) than for either the high-dose or low-dose KCl treatments (0.44 ± 0.53 for each), but was not significantly different from that of the low-dose KPEN treatment (1.4 ± 1.13). When the number of defecations for the high-dose and low-dose KPEN treatments was combined and compared with that of combined high-dose and low-dose KCl treatments, a significant difference was found in the number of defecations between KPEN treatment (1.83 ± 1.34) and KCl treatment (0.44 ± 0.53).

**Activity indices following KCl administration**—When activity indices for the reference period, three 5-minute segments, and four 15-minute segments following low-dose KCl treatment were compared, no significant increases in activity over the reference index developed in either the cecum or pelvic flexure (**Table 1**). Following high-dose KCl treatment, significant increases in activity over the reference index developed only during segment 1 of the three 5-minute segments in the pelvic flexure (**Table 2**).

**Activity indices following KPEN administration**—When activity indices for the three 5-minute segments following low-dose KPEN treatment were analyzed, significant increases in activity over the reference index developed during segment 1 in the cecum and pelvic flexure (Table 1). For the four 15-minute segments following low-dose KPEN treatment, significant increases in activity over the reference index developed during segment 1 in the pelvic flexure

Table 1—Mean (± SD) values of activity indexes as a percentage of the reference index for portions of the large intestine following IV bolus administration of penicillin G potassium (KPEN) or potassium chloride (KCl) in horses

| | Cecum | | | | Pelvic flexure | | | |
|---|---|---|---|---|---|---|---|---|
| Segments* | Low-dose KCl | High-dose KCl | Low-dose KPEN | High-dose KPEN | Low-dose KCl | High-dose KCl | Low-dose KPEN | High-dose KPEN |
| 1 | 101.5 ± 37.76 | 109.9 ± 78.65 | 126.2 ± 60.71[a] | 124.3 ± 171.91 | 97.9 ± 40.17 | 149.4 ± 106.10[a] | 162.0 ± 61.00[a] | 187.4 ± 140.30[a] |
| 2 | 100.1 ± 52.14 | 85.0 ± 50.28 | 88.0 ± 79.36[b] | 140.1 ± 108.87 | 90.7 ± 56.59 | 82.9 ± 65.18[b] | 118.8 ± 94.60[b] | 149.2 ± 78.70[a,b] |
| 3 | 110.2 ± 42.96 | 105.2 ± 60.29 | 85.4 ± 41.84[b] | 111.6 ± 49.35 | 87.2 ± 56.26 | 113.6 ± 78.37[b] | 88.6 ± 43.54[c] | 127.2 ± 112.72[b,c] |
| Reference | 100.0 | 100.0 | 100.0[b] | 100.0 | 100.0 | 100.0[b] | 100.0[b,c] | 100.0[c] |

*Segment 1 represents the period from time 0 to 5 minutes after treatment, segment 2 represents the period from 5 to 10 minutes after treatment, and segment 3 represents the period from 10 to 15 minutes after treatment.
[a,b,c]Values with different superscript letters within a column are significantly ($P < 0.05$) different from each other.
Low-dose KCl = 17 mEq of KCl. High-dose KCl = 34 mEq of KCl. Low-dose KPEN = $1 \times 10^7$ U of KPEN. High-dose KPEN = $2 \times 10^7$ U of KPEN.

Table 2—Mean (± SD) values of activity indexes as a percentage of the reference index for portions of the large intestine following IV bolus administration of KPEN or KCl in horses

| | Cecum | | | | Pelvic flexure | | | |
|---|---|---|---|---|---|---|---|---|
| Segments* | Low-dose KCl | High-dose KCl | Low-dose KPEN | High-dose KPEN | Low-dose KCl | High-dose KCl | Low-dose KPEN | High-dose KPEN |
| 1 | 104.1 ± 27.24 | 100.0 ± 38.49 | 100.0 ± 26.76 | 125.3 ± 71.38 | 91.9 ± 39.03 | 115.3 ± 49.58 | 123.0 ± 37.13[a] | 154.6 ± 92.83[a] |
| 2 | 107.3 ± 49.15 | 161.8 ± 178.43 | 94.8 ± 74.66 | 109.2 ± 94.02 | 95.0 ± 49.68 | 107.3 ± 65.23 | 87.0 ± 39.67[b] | 144.3 ± 112.45[a,b] |
| 3 | 105.4 ± 40.26 | 213.0 ± 285.60 | 98.7 ± 56.66 | 99.2 ± 46.13 | 92.5 ± 49.59 | 105.5 ± 44.21 | 90.5 ± 41.29[b] | 141.5 ± 83.80[a,b] |
| 4 | 102.0 ± 42.13 | 177.4 ± 156.87 | 102.7 ± 59.00 | 98.2 ± 49.31 | 86.2 ± 38.30 | 107.6 ± 39.92 | 96.3 ± 61.17[b] | 115.2 ± 70.56[b,c] |
| Reference | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0[b] | 100.0[c] |

*Segment 1 represents the period from time 0 to 15 minutes after treatment, segment 2 represents the period from 15 to 30 minutes after treatment, segment 3 represents the period from 30 to 45 minutes after treatment, and segment 4 represents the period from 45 to 60 minutes after treatment.
*See* Table 1 for remainder of key.

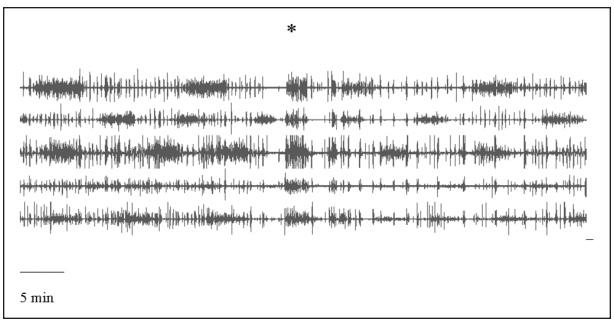


Figure 1—Representative tracings of a colonic migrating myoelectric complex (*) that developed in the pelvic flexure of a horse immediately after IV bolus administration of penicillin G potassium.

(Table 2). When activity indices for the three 5-minute segments following high-dose KPEN treatment were analyzed, significant increases in activity over the reference index developed during segments 1 and 2 in the pelvic flexure. For the four 15-minute segments following high-dose KPEN treatment, significant increases in activity over the reference index developed during segments 1, 2, and 3 in the pelvic flexure.

**CMMCs—**A total of 14 CMMCs were recorded during the twenty-seven 10-minute periods immediately following treatments (**Fig 1**), and 14 were recorded during the other 270 periods. The CMMCs were significantly more likely in segments immediately following high-dose KPEN treatment (7/7) and low-dose KPEN treatment (5/7) than during the other segments of the corresponding recording sessions (2/70 and 6/70, respectively). The CMMCs were not significantly more likely in the segments immediately following high-dose KCl treatment (2/7) or low-dose KCl treatment (0/6) than during the other segments of the corresponding recording sessions (5/70 and 3/60, respectively).

## Discussion

In our study, IV administration of KPEN at either treatment dose resulted in increased defecation in the 15 minutes following injection. This was probably caused by direct or neurally mediated stimulation of smooth muscle in the small colon and rectum. Myoelectric activity increased in the pelvic flexure and, to a lesser extent, in the cecum after IV administration of KPEN; myoelectric activity only increased in the pelvic flexure immediately after IV administration of KCl. Although the experiment was not designed to evaluate a dose response, the higher dose of KPEN was more effective at stimulating motility than the lower dose. The doses administered were chosen because they are the most frequently used doses in our hospital during the postoperative period. The exact mechanism by which KPEN stimulates defecation and large-intestinal motility could not be determined in our study. Increasing the concentration of extracellular potassium lowers membrane resting potential, thus increasing the excitability of smooth muscle cells. It seemed conceivable to us that the injection of a bolus of $K^+$ might stimulate a contractile event in the smooth muscle of the intestine. For this reason, we administered equimolar quantities of potassium ion in the form of KPEN or KCl to the horses. Except for a single 5-minute segment in the pelvic flexure, no response in the activity index to KCl was found. The single event could have occurred by chance. Therefore, our results indicate

that the penicillin, not the $K^+$, is required for the effect. We cannot, however, rule out the possibility of an interaction between potassium and penicillin whereby both are required for the effect to occur.

The induction of CMMCs by KPEN administration was somewhat surprising. Induction of CMMCs by erythromycin administration has previously been attributed to motilin-like activity and was thought to be evidence of motilin receptors in the pelvic flexure of horses.[d] There are no published reports indicating that penicillin stimulates motilin receptors in other species. If motilin receptors are not involved, it is possible that erythromycin and penicillin both induce CMMCs through a different common pathway, but this has not been described.

Penicillin did not stimulate smooth muscle contraction in the rabbit jejunum in vitro. However, this does not imply that equine colonic smooth muscle tissue is not responsive to penicillin. For example, with erythromycin, there are differences in response between in vivo and in vitro experiments, among regions of the gastrointestinal tract, and among species.[4-8, 14,d]

On the basis of our results, the pelvic flexure appears to be more sensitive than the cecum to KPEN. From the apparent greater sensitivity of the pelvic flexure over the cecum and the consistent response of the small colon and rectum, it may be proposed that a gradient of sensitivity to KPEN exists, with the greater sensitivity being in the aborad portion of the large intestine.

Results of our study indicate that KPEN has prokinetic effects on the small colon and rectum of horses when administered IV. This probably explains the frequent occurrence of defecation following therapeutic injection of KPEN that has been anecdotally described. If KPEN has prokinetic effects in horses with ileus, it could help ameliorate reduced postoperative fecal output,[15] a type of large-intestinal postoperative ileus. Conversely, in horses with diarrhea, KPEN could increase colonic evacuation and fecal output, which could possibly increase fluid loss. Therefore, depending on the medical condition of horses, the motility-modifying effects of KPEN should be considered.

[a]WINDAQ 200, Dataq Instruments Inc, Akron, Ohio.
[b]Iomega Zip Discs, Iomega Corp, Roy, Utah.
[c]WINDAQ Playback, Dataq Instruments Inc, Akron, Ohio.
[d]Masri MD, Merritt AM, Burrow JA. Effect of erythromycin on equine colonic motility (abstr), in *Proceedings*. Am Motil Soc Biannu Meet 1990;113.

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